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09/581,500	11/14/2000	Christine Van Broeckhoven	B0192/7019	9967

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EXAMINER	
JOHANNSEN, DIANA B	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/581,500	VAN BROECKHOVEN ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 & 05 November 2003; 06 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,20,25-27 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,20,25-27 and 29* is/are rejected.

7)☒ Claim(s) *20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 June 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL REJECTION

1. This action is in response to the Amendment filed November 3, 2003, and the Amendment (including a complying complete set of claims) filed February 6, 2004. It is noted that the reference filed by FAX on November 5, 2003 (supplementary to the Amendment of November 3, 2003) has also been received and entered. Claims 11-19, 21-24, 28, and 30-47 have been canceled. Claims 1-10, 20, 25-27, and 29 have been amended and are now under consideration. Applicants' amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn as being obviated by Applicants' amendments. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

3. It is noted that claims 11-19, 21-24, and 33-47, which were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, have now been canceled. Election was made **without** traverse in the Response of December 2, 2002. Further, claims 30-32 (drawn to non-elected sequences), which were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, have now been canceled. Election of the sequences of Figures 15a-b was made **without** traverse in the Response of March 24, 2003.

Oath/Declaration

4. It is again noted that the oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because it improperly claims priority to the PCT application of which it is a 371. As the instant application is a 371 of PCT/EP98/08543, a priority claim to the PCT application is not proper.

It is noted that Applicants have indicated in their Remarks that a new oath/declaration has been prepared and will be submitted when it has been executed.

Specification

THE FOLLOWING ARE NEW GROUNDS OF OBJECTION NECESSITATED BY APPLICANTS' AMENDMENTS:

5. The amendment filed November 5, 2003 (a copy of which was also provided on February 6, 2004) is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material that is not supported by the original disclosure is as follows. At pages 25-26, 29, and 32, Applicant has added to the specification names and addresses of organizations corresponding to hyperlinks that have been deleted from the specification. However, as Applicant has not provided declaratory evidence that the added names/addresses actually corresponded to the deleted hyperlinks at the time the invention was made (i.e., as of the filing of the application), this amendment introduces new matter into the specification.

Applicant is required to cancel the new matter in the reply to this Office Action. Alternatively, Applicant may either provide declaratory evidence as discussed above, or delete the added names/addresses and replace them with the previously recited web addresses lacking the previously recited "http://" so as to provide web addresses rather than embedded hyperlinks.

6. Claim 20 is objected to because a claim to a product does not properly depend from a claim to a method in which that product may be used. See MPEP 608.01(n). It is noted that claim 7, from which claim 20 depends, is not drawn to a method of preparing nucleic acids, but rather to a method in which nucleic acids are employed and identified.

Claim Rejections - 35 USC § 112, first paragraph

7. In view of the cancellation of claim 28, the prior rejection of the claim under 35 U.S.C. 112, first paragraph for lack of enablement is moot.

8. Claims 1-10, 20, 25-27, and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons stated in the Office action of July 1, 2003.

It is noted that claims 1-10, 20, 25-27, and 29 have been amended. However, the claims remain rejection for reasons that were set forth in the prior Office action. In particular, it is again noted that neither the specification nor the art provide evidence that any of the nucleic acids or markers of the claims are actually associated with

bipolar disorder or any other "mood disorder or related disorder." As no such association has been established, it is unpredictable as to whether one of skill in the art could actually practice the claimed invention, and it would require undue experimentation to use the invention of the claims.

The response traverses the rejection on the following grounds.

a) First, Applicant argues that "the association between the region of chromosome 18q and mood disorder is supported in the specification at page 4, lines 10 to 22, which describes a study in which LOD score analysis was performed on family MAD 31, a Belgian family of a BPII proband." The response states that "Although multi-point linkage analysis gave a maximum multi-point LOD score of +1.34, simulation studies indicated that this LOD score is well within the range of what can be expected for a linked marker given the information available in this family." The response also notes that "the specification also states at page 4 lines 22-30 that 'an affected sib-pair analysis also rejected the null-hypothesis of nonlinkage for several of the markers tested' and 'two other groups also found evidence for linkage of bipolar disorders to 18q." The response urges that "the clear increase in LOD score values observed between the markers D18S346 and D18S979 (shown in Table 2) was considered a significant linkage at the time of filing."

These arguments have been thoroughly considered but are not persuasive. As discussed in the prior Office action, the specification teaches that "A LOD score of 3 (or likelihood ratio of 1000 or greater) is taken as significant statistical evidence for linkage" (page 4), which teaching is completely consistent with the teachings of the prior art as

exemplified by Kahl (page 268 of the *Dictionary of Gene Technology*, VCH, Winheim, 1995). Thus, the teachings of Applicant's own specification (as well as those of the prior art) indicate that a LOD score of 1.34 should not be treated as an indication of linkage. With respect to the statements at page 4 of the specification that "Simulation studies indicated that this LOD score is within the range of what can be expected for a linked marker given the information available in the family" and that "an affected sib-pair analysis also rejected the null-hypothesis of nonlinkage for several of the markers tested," these statements are far from conclusive, and no data from either the simulation studies or the sib-pair analysis are actually reported in the specification. While these teachings suggest that there is a possibility of linkage, actually evidence of such linkage is not provided. With regard to the Freimer et al and Coon et al references cited at page 4 of the specification and referred to in Applicant's response, it is noted that copies of these references have not been provided. Thus, while Applicant asserts that the references "provide evidence for linkage," any such evidence that may be provided by the references cannot be evaluated. With regard to the LOD score values reported in Table 2, it is again noted that none of the scores reported meet the 3.00 threshold specified in the specification and supported by the art. Thus, Applicant's arguments are not persuasive.

b) Next, with regard to the Goossens et al reference, the response argues that the reference "deals only with a possible involvement of triplet nucleotide repeats, i.e., CAG/CTG repeats in bi-polar disorder, but the reference does not question the association of the 8.9 cM region with bi-polar disorder." Thus, the response urges that

"the Goossens reference does not indicate a lack of an association between the region of chromosome 18q region cited in the instant claims and mood disorder."

These arguments have been thoroughly considered but are not persuasive. The Goossens reference does in fact call into question an association between the 8.9 cM region and bi-polar disorder, as the repeats examined by Goossens et al are located in this region (see page 385). While the reference suggests at page 388 that expanded repeats in a different region of chromosome 18 or elsewhere in the genome may be associated with bipolar disorder, the teachings of the reference indicate a lack of such an association with the 8.9 cM region studied. Further, as bi-polar disorder is a mood disorder, the reference further suggests that an association between this region and mood disorders is lacking. Accordingly, these arguments are not persuasive.

c) Finally, the response presents arguments pertaining to the enablement of the claims with respect to various types of mood disorders. However, Applicant's arguments are again reliant on data obtained with the above-referenced MAD31 family; as discussed in section a), above, the data reported for this family does not provide evidence of a significant association with any mood disorder. Accordingly, Applicant's arguments are not persuasive, for the same reasons set forth above. It is also noted that Johns Hopkins reference provided by Applicants has been considered. However, while this reference teaches that many mood disorders are inherited together, the reference is silent with respect to any mood disorders (whether inherited together or not) that are associated with the chromosomal regions of the instant claims, and are further silent with respect to the MAD31 family. It is also noted that as the reference

was published subsequent to the filing date of the instant application, it cannot be relied upon to establish enablement as of the time the instant invention was made.

For all of the reasons given above Applicant's arguments are not persuasive, and therefore this rejection is maintained.

9. Claims 4-5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons stated in the Office action of July 1, 2003.

The response traverses the rejection on the grounds that "the YAC clones referred to in the present application were all publicly available at the priority date of the present application and were obtained from the YAC Screening Centre, Leiden, The Netherlands or from CEPH, Paris, France." The response further states that "In these public collections the YAC clones are referred to using the nomenclature used in claims 4 and 5." The response concludes that "based on the teaching provided in the specification as filed, one of ordinary skill in the art would be able to obtain any of the YAC clones referred to in present claims 4 and 5."

These arguments have been thoroughly considered but are not persuasive. It is acknowledged that page 26 of the specification does state that "CEPH mega-YACs were obtained from the YAC Screening Center Leiden (YSCL, the Netherlands) and from CEPH (Paris, France)." However, Applicant has not adequately established that the YACs of claims 4-5 are known and readily available, as required by *MPEP* 2404.01.

For example, as was the case in *Ex parte Humphreys*, 24 USPQ2d 1255 (Bd. Pat. App. & Int. 1992), Applicants have not made of record "any of the facts and circumstances surrounding their access to the material" or provided "evidence as to the depository's policy regarding the material" (MPEP 2404.01). While Applicant's response asserts that the YAC's of the claims are available from the sources noted in the specification and are referenced by the nomenclature of the claims, no evidence of this has been provided. MPEP 2404.01 states that "The Office will accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material." As Applicant has yet to provide such clear and convincing evidence, Applicant's arguments are not persuasive, and this rejection is maintained.

Claim Rejections - 35 USC § 112, second paragraph

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS' AMENDMENTS:

10. Claims 1-10, 20, 25-27, and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 6 are indefinite over the recitation of the limitation "the equivalent regions of DNA from a person afflicted with a mood disorder or a related disorder" in claim 1. There is insufficient antecedent basis for this limitation in the claims.

Claims 1 and 6 are indefinite over the recitation of the terms "equivalent regions of DNA" and "equivalent regions in the DNA" in claim 1. A definition of the term

"equivalent regions" is not provided either in the specification or in the art, and it is not clear what properties (structural and/or functional) would be required in order for it to be considered "equivalent." Thus, this terminology does not apprise one of skill in the art of the nature of the molecules with which the recited "coding regions/genes" or fragments of the claims are compared. It is further noted that it is not clear whether the "identifying" and "detecting" steps of the claims require the same or different "equivalent regions." Clarification is required.

Claims 1 and 6 are indefinite over the recitation of the phrase "wherein a difference in the coding regions/genes is an indication that the coding region/gene or mutated or polymorphic variant thereof is associated with the mood disorder or related disorder" in claim 1. It is first noted that there is insufficient antecedent basis for the recitation "the coding region/gene or mutated or polymorphic variant thereof" (as the claim does not previous refer to a single "coding region/gene or mutated or polymorphic variant thereof"). Second, it is unclear as to why/how a difference between a "coding region/gene or mutated or polymorphic variant thereof" and an "equivalent region" in an individual "afflicted with a mood disorder or related disorder" would be indicative that the "coding region/gene or mutated or polymorphic variant thereof" is associated with the disorder. In other words, why would one expect a version of a gene that differs from that present in the individual with the disorder to be associated with the disorder (as opposed to the version that is present in the individual with the disorder)? Finally, it is unclear whether the claims are drawn to methods detecting differences in genes (as indicated by this language in the final step of claim 1) or to methods of "identifying"

genes associated with a disorder, as indicated in the claim preamble. Clarification is required.

Claims 2-5 are indefinite over the recitation of the limitation "the equivalent regions of DNA from a person afflicted with a mood disorder or a related disorder" in claim 2. There is insufficient antecedent basis for this limitation in the claims.

Claims 2-5 are indefinite over the recitation of the terms "equivalent regions of DNA" and "equivalent regions in the DNA" in claim 2. A definition of the term "equivalent regions" is not provided either in the specification or in the art, and it is not clear what properties (structural and/or functional) would be required in order for it to be considered "equivalent." Thus, this terminology does not apprise one of skill in the art of the nature of the molecules with which the recited "coding regions/genes" or fragments of the claims are compared. It is further noted that it is not clear whether the "identifying" and "detecting" steps of the claims require the same or different "equivalent regions." Clarification is required.

Claims 2-5 are indefinite over the recitation of the phrase "wherein a difference in the coding regions/genes is an indication that the coding region/gene or mutated or polymorphic variant thereof is associated with the mood disorder or related disorder" in claim 2. It is first noted that there is insufficient antecedent basis for the recitation "the coding region/gene or mutated or polymorphic variant thereof" (as the claim does not previously refer to a single "coding region/gene or mutated or polymorphic variant thereof"). Second, it is unclear as to why/how a difference between a "coding region/gene or mutated or polymorphic variant thereof" and an "equivalent region" in an

individual "afflicted with a mood disorder or related disorder" would be indicative that the "coding region/gene or mutated or polymorphic variant thereof" is associated with the disorder. In other words, why would one expect a version of a gene that differs from that present in the individual with the disorder to be associated with the disorder (as opposed to the version that is present in the individual with the disorder)? Finally, it is unclear whether the claims are drawn to methods of detecting differences in genes (as indicated by this language in the final step of claim 2) or to methods of "identifying" genes associated with a disorder, as indicated in the claim preamble. Clarification is required.

Claims 7, 9-10, and 20 are indefinite because it is unclear whether the claims are drawn to methods of "identifying" a gene associated with a mood disorder or related disorder, as required by the preamble of claim 7, or to a method of "detecting" a gene associated with a mood disorder or related disorder, as required by the method step of the claim. The language of the claims does not indicate how detecting the presence of a gene containing triplet repeats allows one to actually identify that gene. Clarification is required.

Claim 8 is indefinite because it is unclear whether the claim is drawn to a method of identifying a gene (as indicated by the claim preamble), or to a method of comparing sequences and identifying differences in sequences, as indicated by the final step of the claim. It is not clear how the final step of the claim results in "identifying" a gene. Clarification is required.

Claim 8 is indefinite over the recitation of the limitation "equivalent region of DNA." A definition of the term "equivalent region" is not provided either in the specification or in the art, and it is not clear what properties (structural and/or functional) would be required in order for a region of DNA to be considered "equivalent" to another molecule/sequence. Thus, this terminology does not apprise one of skill in the art of the nature of the molecules with which the recited "sequence" is compared.

Claim 8 is indefinite over the recitation of the limitation "wherein a difference in the sequence flanking the triplet repeats and the DNA from the afflicted person is an indication of a human gene or mutated or polymorphic variant thereof that is associated with the mood disorder or related disorder." As it appears that the instant claim encompasses sequences from any YAC clone comprising triplet repeats (as opposed to, e.g., clones containing sequences from particular regions of the human genome in which a gene or genes associated with mood disorders are located), it is unclear as to how a comparison of such clones with any "equivalent region of DNA" from a person with a mood disorder or related disorder and identification of any "differences" in sequence would allow one to identify genes associated with the mood disorder or related disorder. One of skill would expect to identify numerous sequence differences when making such a comparison, with no expectation that differences in sequence would relate to a disorder. Clarification is therefore required.

Claims 9-10 are indefinite over the recitation of the limitation "said triplet repeat" in claim 9 because there is insufficient antecedent basis for this limitation in claim 7, from which claim 9 depends. It is further noted that while this recitation in claim 9

provides basis for the recitation "said triplet repeat" in claim 10, amendment of claim 9 may further necessitate amendment of claim 10.

Claim 20 is indefinite over the recitation of the limitation "a probe of at least 14 contiguous nucleotides of a cDNA obtained by the method of claim 7." As claim 7 is not drawn, e.g., to a method of obtaining or isolating cDNA or any other type of nucleic acid molecule, it is unclear as to what type of probe is encompassed by this recitation. Clarification is required.

Claim 20 is indefinite because it is unclear why "a difference in the hybridization of the probe in the patient" would be considered indicative of "a pathological mutation or genetic variation associated with a mood disorder or related disorder." It is noted that the claim requires merely a "control individual," without specifying a particular type of control (e.g., a control individual with a mood disorder, a control individual without a mood disorder, etc.). Accordingly, it is unclear how a difference in hybridization would allow one to conclude that a mutation or variation associated with a mood disorder is present.

Claims 25-27 and 29 are indefinite because it is unclear as to how the steps of amplifying DNA from a control individual and comparing amplification reaction results relates to determining the presence of "an amplified product that includes a DNA polymorphism associated with a mood disorder or related disorder." The language of the claims does not make clear how the steps performed actually relate to identification of such a product. Clarification is required.

Claims 25-27 and 29 are indefinite over the recitation of the phrase "related disorder of said individual." It is not clear whether this recitation is intended to indicate the presence of susceptibility "to a mood disorder or related disorder" in said individual, or simply to refer to a disorder "of said individual." Clarification is required.

Claim 29 is indefinite over the recitation of the limitation "said nucleotide sequence to be amplified" because there is insufficient antecedent basis for this limitation in claim 25.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is

571/272-0744. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 571/272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Diana B. Johannsen
Patent Examiner
May 12, 2004

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